CLAIMS

1. A method for the treatment of non-insulin dependent diabetes mellitus in a mammal in need of such treatment comprising the repeated administration over an extended period of time of a compound with prolonged action after each administration, said prolonged action necessary to achieve sustained glycemic control in mammals, said compound selected from the group consisting of:

(a) a peptide having the amino acid sequence:
His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Arg-Gly; (SEQUENCE ID NO: 2)

(b) a peptide having the amino acid sequence:
His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-X (SEQUENCE ID NO: 7)
wherein X is selected from the group consisting of:

(A) Lys,

(B) Lys-Gly, and

(C) Lys-Gly-Arg;

(c) a derivative of a polypeptide comprising the primary structure

H_2N-W-COOH

wherein W is an amino acid sequence selected from the group consisting of
His-Asp-Glu-Phe-Glu-Arg-His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Arg-Gly (SEQUENCE ID NO: 1) and
His-Asp-Glu-Phe-Glu-Arg-His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Arg (SEQUENCE ID NO: 6)
which derivative when processed in a mammal results in a polypeptide derivative having an insulinotropic activity;

(d) a derivative of a polypeptide comprising the primary structure

H_2N-R-COOH

wherein R is an amino acid sequence selected from the group consisting of
His-Ala-Glu-Gly-Thr-Ph -Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Arg-Gly; (SEQUENCE ID NO: 2)

His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Arg; (SEQUENCE ID NO: 3)

His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly; (SEQUENCE ID NO: 4) and

His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys; (SEQUENCE ID NO: 5)

and

(e) a derivative of said peptides (a) through (d) wherein said derivative is selected from the group consisting of:

(1) a pharmaceutically acceptable acid addition salt of said peptides;

(2) a pharmaceutically acceptable carboxylate salt of said peptides;

(3) a pharmaceutically acceptable alkali addition salt of said peptides;

(4) a pharmaceutically acceptable lower alkyl ester of said peptides; and

(5) a pharmaceutically acceptable amide of said peptides wherein said pharmaceutically acceptable amide is selected from the group consisting of amide, lower alkyl amide and lower dialkyl amide.

2. The method of claim 1 wherein said administration is subcutaneous.

3. The method of claim 1 wherein said administration is intramuscular.

4. The method of claim 1 wherein said administration is transdermal.

5. The method of claim 1 wherein said administration is by an infusion pump.

6. The method of claim 1 wherein said administration is by oral inhalation.

7. The method of claim 1 wherein said administration is by nasal inhalation.

8. The method of claim 1 wherein said administration is gastrointestinal.

9. A composition of matter comprising;

(i) a compound selected from the group consisting of:

(a) a peptide having the amino acid sequence:

His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Arg-Gly; (SEQUENCE ID NO: 2)

(b) a peptide having the amino acid sequence:

His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-X (SEQUENCE ID NO: 7)

wherein X is selected from the group consisting of:

(A) Lys,

(B) Lys-Gly,

(C) Lys-Gly-Arg;

(c) a derivative of a polypeptide comprising the primary structure

H_2N-W-COOH

wherein W is an amino acid sequence selected from the group consisting of

His-Asp-Glu-Phe-Glu-Arg-His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Arg-Gly (SEQUENCE ID NO: 1) and

His-Asp-Glu-Phe-Glu-Arg-His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Arg (SEQUENCE ID NO: 6)

which derivative when processed in a mammal results in a polypeptide derivative having an insulinotropic activity;

(d) a derivative of a polypeptide comprising the primary structure

H_2N-R-COOH

wherein R is an amino acid sequence selected from the group consisting of

His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Arg-Gly (SEQUENCE ID NO: 2)

His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Arg (SEQUENCE ID NO: 3)

His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly (SEQUENCE ID NO: 4) and

His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys; (SEQUENCE ID NO: 5)

a derivative of said peptides (a) through (d) wherein said derivative is selected from the group consisting of:

(1) a pharmaceutically acceptable acid addition salt of said peptides;

(2) a pharmaceutically acceptable carboxylate salt of said peptides;

(3) a pharmaceutically acceptable alkali addition salt of said peptides;

(4) a pharmaceutically acceptable lower alkyl ester of said peptides; and

(5) a pharmaceutically acceptable amide of said peptides wherein said pharmaceutically acceptable amide is selected from the group consisting of amide, lower alkyl amide and lower dialkyl amide, and

(ii) a polymer capable of prolonging the action of said compound to achieve sustained glycemic control.

10. A composition according to claim 9 wherein said polymer is a low molecular weight polymer.

11. A composition according to claim 9 wherein said polymer is selected from the group consisting of polyethylene glycol, polyvinylpyrrolidone, polyvinylalcohol, polyoxyethylene-polyoxypropylene copolymers, polysaccharides selected from the group consisting of cellulose, cellulose derivatives, chitosan, acacia gum, karaya gum, guar gum, xanthan gum, tragacanth, alginic acid, carrageenan, agarose, and furcellarans, dextran, starch, starch derivatives, hyaluronic acid, polyesters, polyamides, polyanhydrides, and polyortho esters.

12. A composition according to claim 11 wherein said polymer is selected from the group consisting of polyethylene glycol and polyvinylpyrrolidone.

13. A composition of matter comprising;

(i) a compound selected from the group consisting of:

(a) a peptide having the amino acid sequence:

His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Arg-Gly; (SEQUENCE ID NO: 2)

(b) a peptide having the amino acid sequence:

His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-X (SEQUENCE ID NO: 7)

wherein X is selected from the group consisting of:

(A) Lys,

(B) Lys-Gly, and

(C) Lys-Gly-Arg;

(c) a derivative of a polypeptide comprising the primary structure

H_2N-W-COOH

wherein W is an amino acid sequence selected from the group consisting of

His-Asp-Glu-Phe-Glu-Arg-His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Arg-Gly (SEQUENCE ID NO: 1) and

His-Asp-Glu-Phe-Glu-Arg-His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Arg (SEQUENCE ID NO: 6)

which derivative when processed in a mammal results in a polypeptide derivative having an insulinotropic activity;

(d) a derivative of a polypeptide comprising the primary structure

H_2N-R-COOH

wherein R is an amino acid sequence selected from the group consisting of

His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Arg-Gly; (SEQUENCE ID NO: 2)

His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Arg; (SEQUENCE ID NO: 3)

His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly; (SEQUENCE ID NO: 4) and

His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys; (SEQUENCE ID NO: 5)

and

a derivative of said peptides (a) through (d) wherein said derivative is selected from the group consisting of:

(1) a pharmaceutically acceptable acid addition salt of said peptides;

(2) a pharmaceutically acceptable carboxylate salt of said peptides;

(3) a pharmaceutically acceptable alkali addition salt of said peptides;

(4) a pharmaceutically acceptable lower alkyl ester of said peptides; and

(5) a pharmaceutically acceptable amide of said peptides wherein said pharmaceutically acceptable amide is selected from the group consisting of amide, lower alkyl amide and lower dialkyl amide, and

(ii) a pharmaceutically acceptable water-immiscible oil suspension capable of prolonging action of said compound to achieve sustained glycemic control.

14. A composition according to claim 13 wherein said oil is selected from the group consisting of peanut oil, sesame oil, almond oil, castor oil, camellia oil, cotton

seed oil, olive oil, corn oil, soy oil, safflower oil, coconut oil, and esters of fatty acids, esters of fatty alcohols.

15. A composition according to claim 13 further comprising a wetting agent.

16. A composition according to claim 15 wherein said wetting agent is a nonionic surfactant.

17. A composition according to claim 13 further comprising a suspending agent.

18. A composition of matter comprising;

(i) a compound selected from the group consisting of:

(a) a peptide having the amino acid sequence:
His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Arg-Gly; (SEQUENCE ID NO: 2)

(b) a peptide having the amino acid sequence:
His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-X (SEQUENCE ID NO: 7)
wherein X is selected from the group consisting of:

(A) Lys,

(B) Lys-Gly, and

(C) Lys-Gly-Arg;

(c) a derivative of a polypeptide comprising the primary structure

H_2N-W-COOH

wherein W is an amino acid sequence selected from the group consisting of
His-Asp-Glu-Phe-Glu-Arg-His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Arg-Gly (SEQUENCE ID NO: 1) and
His-Asp-Glu-Phe-Glu-Arg-His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Arg (SEQUENCE ID NO: 6)
which derivative when processed in a mammal results in a polypeptide derivative having an insulinotropic activity;

(d) a derivative of a polypeptide comprising the primary structure

H_2N-R-COOH

wherein R is an amino acid sequence selected from the group consisting of

His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Arg-Gly (SEQUENCE ID NO: 2)

His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Arg (SEQUENCE ID NO: 3)

His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly (SEQUENCE ID NO: 4) and

His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys (SEQUENCE ID NO: 5);

and

a derivative of said peptides (a) through (d) wherein said derivative is selected from the group consisting of:

(1) a pharmaceutically acceptable acid addition salt of said peptides;

(2) a pharmaceutically acceptable carboxylate salt of said peptides;

(3) a pharmaceutically acceptable alkali addition salt of said peptides;

(4) a pharmaceutically acceptable lower alkyl ester of said peptides; and

(5) a pharmaceutically acceptable amide of said peptides wherein said pharmaceutically acceptable amide is selected from the group consisting of amide, lower alkyl amide and lower dialkyl amide, and

(ii) zinc (II), which is complexed with the peptide.

19. A composition according to claim 18 capable of achieving sustained glycemic control.

20. A composition according to claim 18 which is amorphous.

21. A composition according to claim 18 which is crystalline.

22. A composition according to claim 18 which is an aqueous suspension.

23. A composition of matter comprising;

(i) a compound selected from the group consisting of:

(a) a peptide having the amino acid sequence:

His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Arg-Gly; (SEQUENCE ID NO: 2)

(b) a peptide having the amino acid sequence:

His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-X (SEQUENCE ID NO: 7)

wherein X is selected from the group consisting of:

(A) Lys,

(B) Lys-Gly, and

(C) Lys-Gly-Arg;

(c) a derivative of a polypeptide comprising the primary structure

H_2N-W-COOH

wherein W is an amino acid sequence selected from the group consisting of

His-Asp-Glu-Phe-Glu-Arg-His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Arg-Gly (SEQUENCE ID NO: 1) and

His-Asp-Glu-Phe-Glu-Arg-His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Arg (SEQUENCE ID NO: 6

which derivative when processed in a mammal results in a polypeptide derivative having an insulinotropic activity;

(d) a derivative of a polypeptide comprising the primary structure

H_2N-R-COOH

wherein R is an amino acid sequence selected from the group consisting of

His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Arg-Gly (SEQUENCE ID NO: 2)

His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Arg (SEQUENCE ID NO: 3)

His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly (SEQUENCE ID NO: 4) and

His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys (SEQUENCE ID NO: 5);

and

a derivative of said peptides (a) through (d) wherein said derivative is selected from the group consisting of:

(1) a pharmaceutically acceptable acid addition salt of said peptides;

(2) a pharmaceutically acceptable carboxylate salt of said peptides;

(3) a pharmaceutically acceptable alkali addition salt of said peptides;

(4) a pharmaceutically acceptable lower alkyl ester of said peptides; and

(5) a pharmaceutically acceptable amide of said peptides wherein said pharmaceutically acceptable amide is selected from the group consisting of amide, lower alkyl amide and lower dialkyl amide, and

(ii) a metal selected from the group consisting of Ni (II), Co (II), Mg (II), Ca (II), K (I), Mn (II), Fe(II), and Cu(II).

24. A composition according to claim 23 capable of achieving sustained glycemic control.

25. A composition of matter comprising;

(i) a compound selected from the group consisting of:

(a) a peptide having the amino acid sequence:
His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Arg-Gly; (SEQUENCE ID NO: 2)

(b) a peptide having the amino acid sequence:
His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-X (SEQUENCE ID NO: 7)
wherein X is selected from the group consisting of:

(A) Lys,

(B) Lys-Gly, and

(C) Lys-Gly-Arg;

(c) a derivative of a polypeptide comprising the primary structure

H_2N-W-COOH

wherein W is an amino acid sequence selected from the group consisting of
His-Asp-Glu-Phe-Glu-Arg-His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Arg-Gly (SEQUENCE ID NO: 1) and
His-Asp-Glu-Phe-Glu-Arg-His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Arg (SEQUENCE ID NO: 6)
which derivative when processed in a mammal results in a polypeptide derivative having an insulinotropic activity;

(d) a derivative of a polypeptide comprising the primary structure

H_2N-R-COOH

wherein R is an amino acid sequence selected from the group consisting of

His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Arg-Gly; (SEQUENCE ID NO: 2)

His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Arg; (SEQUENCE ID NO: 3)

His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly; (SEQUENCE ID NO: 4) and

His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys; (SEQUENCE ID NO: 5)

and

a derivative of said peptides (a) through (d) wherein said derivative is selected from the group consisting of:

(1) a pharmaceutically acceptable acid addition salt of said peptides;

(2) a pharmaceutically acceptable carboxylate salt of said peptides;

(3) a pharmaceutically acceptable alkali addition salt of said peptides;

(4) a pharmaceutically acceptable lower alkyl ester of said peptides; and

(5) a pharmaceutically acceptable amide of said peptides wherein said pharmaceutically acceptable amide is selected from the group consisting of amide, lower alkyl amide and lower dialkyl amide, and

(ii) a basic polypeptide, wherein said composition is an aqueous suspension capable of sustained glycemic control.

26. A composition according to claim 25 wherein said basic polypeptide is protamine.

27. A composition of matter comprising;

(i) a compound selected from the group consisting of:

(a) a peptide having the amino acid sequence:

His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Arg-Gly (SEQUENCE ID NO: 2);

(b) a peptide having the amino acid sequence:

His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-X (SEQUENCE ID NO: 7)

wherein X is selected from the group consisting of:

(A) Lys,

(B) Lys-Gly,

(C) Lys-Gly-Arg;

(c) a derivative of a polypeptide comprising the primary structure

H_2N-W-COOH

wherein W is an amino acid sequence selected from the group consisting of

His-Asp-Glu-Phe-Glu-Arg-His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Arg-Gly (SEQUENCE ID NO: 1) and

His-Asp-Glu-Phe-Glu-Arg-His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Arg (SEQUENCE ID NO: 6)

which derivative when processed in a mammal results in a polypeptide derivative having an insulinotropic activity;

(d) a derivative of a polypeptide comprising the primary structure

H_2N-R-COOH

wherein R is an amino acid sequence selected from the group consisting of

His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Arg-Gly (SEQUENCE ID NO: 2);

His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Arg (SEQUENCE ID NO: 3);

His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly (SEQUENCE ID NO: 4); and

His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys (SEQUENCE ID NO: 5);

and

a derivative of said peptides (a) through (d) wherein said derivative is selected from the group consisting of:

(1) a pharmaceutically acceptable acid addition salt of said peptides;

(2) a pharmaceutically acceptable carboxylate salt of said peptides;

(3) a pharmaceutically acceptable alkali addition salt of said peptides;

(4) a pharmaceutically acceptable lower alkyl ester of said peptides; and

(5) a pharmaceutically acceptable amide of said peptides wherein said pharmaceutically acceptable amide is selected from the group consisting of amide, lower alkyl amide and lower dialkyl amide, and

(ii) a phenolic compound, wherein said composition is an aqueous suspension capable of sustained glycemic control.

28. A composition according to claim 27 wherein said phenolic compound is selected from the group consisting of phenol, cresol, resorcinol, and methyl paraben.

29. A composition of matter comprising;

(i) a compound selected from the group consisting of:

(a) a peptide having the amino acid sequence:
His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Arg-Gly (SEQUENCE ID NO: 2);

(b) a peptide having the amino acid sequence:
His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-X (SEQUENCE ID NO: 7)
wherein X is selected from the group consisting of:

(A) Lys,

(B) Lys-Gly,

(C) Lys-Gly-Arg;

(c) a derivative of a polypeptide comprising the primary structure

H_2N-W-COOH

wherein W is an amino acid sequence selected from the group consisting of
His-Asp-Glu-Phe-Glu-Arg-His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Arg-Gly (SEQUENCE ID NO: 1) and
His-Asp-Glu-Phe-Glu-Arg-His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Arg (SEQUENCE ID NO: 6)
which derivative when processed in a mammal results in a polypeptide derivative having an insulinotropic activity;

(d) a derivative of a polypeptide comprising the primary structure

H_2N-R-COOH

wherein R is an amino acid sequence selected from the group consisting of
His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Arg-Gly (SEQUENCE ID NO: 2);

His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Arg (SEQUENCE ID NO: 3);

His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly (SEQUENCE ID NO: 4); and

His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys (SEQUENCE ID NO: 5);

and

a derivative of said peptides (a) through (d) wherein said derivative is selected from the group consisting of:

(1) a pharmaceutically acceptable acid addition salt of said peptides;

(2) a pharmaceutically acceptable carboxylate salt of said peptides;

(3) a pharmaceutically acceptable alkali addition salt of said peptides;

(4) a pharmaceutically acceptable lower alkyl ester of said peptides; and

(5) a pharmaceutically acceptable amide of said peptides wherein said pharmaceutically acceptable amide is selected from the group consisting of amide, lower alkyl amide and lower dialkyl amide, and

(ii) a basic polypeptide and a phenolic compound, wherein such composition is an aqueous suspension capable of sustained glycemic control.

30. A composition of matter comprising;

(i) a compound selected from the group consisting of:

(a) a peptide having the amino acid sequence:

His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Arg-Gly; (SEQUENCE ID NO: 2)

(b) a peptide having the amino acid sequence:

His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-X (SEQUENCE ID NO: 7)

wherein X is selected from the group consisting of:

(A) Lys,

(B) Lys-Gly, and

(C) Lys-Gly-Arg;

(c) a derivative of a polypeptide comprising the primary structure

H_2N-W-COOH

wherein W is an amino acid sequence selected from the group consisting of

His-Asp-Glu-Phe-Glu-Arg-His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Arg-Gly (SEQUENCE ID NO: 1) and

His-Asp-Glu-Phe-Glu-Arg-His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Arg (SEQUENCE ID NO: 6)

which derivative when processed in a mammal results in a polypeptide derivative having an insulinotropic activity;

(d) a derivative of a polypeptide comprising the primary structure

H_2N-R-COOH

wherein R is an amino acid sequence selected from the group consisting of

His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Arg-Gly; (SEQUENCE ID NO: 2)

His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Arg; (SEQUENCE ID NO: 3)

His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly; (SEQUENCE ID NO: 4) and

His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys; (SEQUENCE ID NO: 5)

and

a derivative of said peptides (a) through (d) wherein said derivative is selected from the group consisting of:

(1) a pharmaceutically acceptable acid addition salt of said peptides;

(2) a pharmaceutically acceptable carboxylate salt of said peptides;

(3) a pharmaceutically acceptable alkali addition salt of said peptides;

(4) a pharmaceutically acceptable lower alkyl ester of said peptides; and

(5) a pharmaceutically acceptable amide of said peptides wherein said pharmaceutically acceptable amide is selected from the group consisting of amide, lower alkyl amide and lower dialkyl amide, and

(ii) a basic polypeptide, a phenolic compound, and a metal ion wherein said composition is an aqueous suspension capable of sustained glycemic control.

31. A composition according to claim 30 wherein said basic polypeptide is protamine.

32. A composition according to claim 30 wherein said metal ion is zinc.

33. A composition of matter comprising;

(i) a compound selected from the group consisting of:

(a) a peptide having the amino acid sequence:

His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Arg-Gly (SEQUENCE ID NO: 2);

(b) a peptide having the amino acid sequence:

His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-X (SEQUENCE ID NO: 7)

wherein X is selected from the group consisting of:

(A) Lys,

(B) Lys-Gly,

(C) Lys-Gly-Arg;

(c) a derivative of a polypeptide comprising the primary structure

H_2N-W-COOH

wherein W is an amino acid sequence selected from the group consisting of

His-Asp-Glu-Phe-Glu-Arg-His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Arg-Gly (SEQUENCE ID NO: 1) and

His-Asp-Glu-Phe-Glu-Arg-His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Arg (SEQUENCE ID NO: 6)

which derivative when processed in a mammal results in a polypeptide derivative having an insulinotropic activity;

(d) a derivative of a polypeptide comprising the primary structure

H_2N-R-COOH

wherein R is an amino acid sequence selected from the group consisting of

His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Arg-Gly (SEQUENCE ID NO: 2);

His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Arg (SEQUENCE ID NO: 3);

His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly (SEQUENCE ID NO: 4); and

His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys (SEQUENCE ID NO: 5);

and

a derivative of said peptides (a) through (d) wherein said derivative is selected from the group consisting of:

(1) a pharmaceutically acceptable acid addition salt of said peptides;

(2) a pharmaceutically acceptable carboxylate salt of said peptides;

(3) a pharmaceutically acceptable alkali addition salt of said peptides;

(4) a pharmaceutically acceptable lower alkyl ester of said peptides; and

(5) a pharmaceutically acceptable amide of said peptides wherein said pharmaceutically acceptable amide is selected from the group consisting of amide, lower alkyl amide and lower dialkyl amide, and

(ii) said peptides and derivatives thereof having being subjected to conditions resulting in amorphous or crystalline material formation.

34. A composition according to claim 33 wherein said conditions are high shear, exposure to salts; or combinations thereof.

35. A composition according to claim 34 wherein said salt is selected from the group consisting of ammonium sulfate, sodium sulfate, lithium sulfate, lithium chloride, sodium citrate, ammonium citrate, sodium phosphate, potassium phosphate, sodium chloride, potassium chloride, ammonium chloride, sodium acetate, ammonium acetate, magnesium sulfate, calcium chloride, ammonium nitrate, and sodium formate; and combinations thereof.

36. A composition of matter comprising;

(i) a compound selected from the group consisting of:

(a) a peptide having the amino acid sequence:

His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Arg-Gly; (SEQUENCE ID NO: 2)

(b) a peptide having the amino acid sequence:

His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-X (SEQUENCE ID NO: 7)

wherein X is selected from the group consisting of:

(A) Lys,

(B) Lys-Gly, and

(C) Lys-Gly-Arg;

(c) a derivative of a polypeptide comprising the primary structure

H_2N-W-COOH

wherein W is an amino acid sequence selected from the group consisting of

His-Asp-Glu-Phe-Glu-Arg-His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Arg-Gly (SEQUENCE ID NO: 1) and

His-Asp-Glu-Phe-Glu-Arg-His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Arg (SEQUENCE ID NO: 6)

which derivative when processed in a mammal results in a polypeptide derivative having an insulinotropic activity;

(d) a derivative of a polypeptide comprising the primary structure

H_2N-R-COOH

wherein R is an amino acid sequence selected from the group consisting of

His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Arg-Gly; (SEQUENCE ID NO: 2)

His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Arg; (SEQUENCE ID NO: 3)

His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly; (SEQUENCE ID NO: 4) and

His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys; (SEQUENCE ID NO: 5)

and

a derivative of said peptides (a) through (d) wherein said derivative is selected from the group consisting of:

(1) a pharmaceutically acceptable acid addition salt of said peptides;

(2) a pharmaceutically acceptable carboxylate salt of said peptides;

(3) a pharmaceutically acceptable alkali addition salt of said peptides;

(4) a pharmaceutically acceptable lower alkyl ester of said peptides; and

(5) a pharmaceutically acceptable amide of said peptides wherein said pharmaceutically acceptable amide is selected from the group consisting of amide, lower alkyl amide and lower dialkyl amide, and

(ii) a liposome delivery system capable of sustained glycemic control.

37. A composition according to claim 36 wherein said liposome is phospholipid based.

38. A composition according to claim 36 wherein said liposome is non-phospholipid based.

39. A method for the treatment of non-insulin dependent diabetes mellitus in a mammal in need of such treatment comprising the prolonged administration of a composition according to claim 9.

40. A method for the treatment of non-insulin dependent diabetes mellitus in a mammal in need of such treatment comprising of the prolonged administration of a composition according to claim 13.

41. A method for the treatment of non-insulin dependent diabetes mellitus in a mammal in need of such treatment comprising of the prolonged administration of a composition according to claim 18.

42. A method for the treatment of non-insulin dependent diabetes mellitus in a mammal in need of such treatment comprising of the prolonged administration of a composition according to claim 23.

43. A method for the treatment of non-insulin dependent diabetes mellitus in a mammal in need of such treatment comprising of the prolonged administration of a composition according to claim 25.

44. A method for the treatment of non-insulin dependent diabetes mellitus in a mammal in need of such treatment comprising of the prolonged administration of a composition according to claim 27.

45. A method for the treatment of non-insulin dependent diabetes mellitus in a mammal in need of such treatment comprising of the prolonged administration of a composition according to claim 29.

46. A method for the treatment of non-insulin dependent diabetes mellitus in a mammal in need of such treatment comprising of the prolonged administration of a composition according to claim 30.

47. A method for the treatment of non-insulin dependent diabetes mellitus in a mammal in need of such treatment comprising of the prolonged administration of a composition according to claim 33.

48. A method for the treatment of non-insulin dependent diabetes mellitus in a mammal in need of such treatment comprising of the prolonged administration of a composition according to claim 36.